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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/674,087	09/29/2003	**Jianzhu Chen**	0492611-0507 (MIT 10396)	2178

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	**PAPER NUMBER**
1635	

NOTIFICATION DATE	DELIVERY MODE
12/29/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@choate.com

Office Action Summary	Application No.	Applicant(s)	
	10/674,087	CHEN ET AL.	
	Examiner	Art Unit	
	KIMBERLY CHONG	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-49,81-90 and 98-102* is/are pending in the application.

4a) Of the above claim(s) *43-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-42,49,81-90,98-102* is/are rejected.

7)☒ Claim(s) *102* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/18/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 09/11/2008 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 03/11/2008 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 38-42, 49, 81-90 and 98-100 are under examination and claims 43-48 and the non-elected subject matter are withdrawn as being drawn to a non-elected invention.

Information Disclosure Statement

The non-patent literature documents Tompkins et al., Verma et al. and Zhang et al. cited on the IDS filed 12/18/2006 have been considered and signed copies indicating the considered references have been placed in the file.

New Claim Objections and Rejections

Claim Objections

Claim 102 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only

and/or cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claim 102 has not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 101 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 101 recites the limitation "The method of any one of claims 38, 49, 81, 84 and 101". A claim cannot reference itself and it appears the reference to "101" is a typographical error and should be "100". For purposes of prior art, claim 101 is being interpreted as such.

Claim Rejections - 35 USC § 103

The new rejection is necessitated by new claim amendments filed 09/11/2008

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 38-42, 49, 81-90 and 98-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abel et al. (European Journal of Pharm. Sci, 2001 of record IDS filed 09/12/2005), Tuschl et al. (WO 02/44321), Astriab-Fisher et al. teach (Biochemical Pharmacology, 2000. Vol. 60, pp.83-90) and Deonarain et al. (Expert Opinion Ther. Patents 1998, Vol. 8(1): 53-69).

The claims are drawn to methods of inhibiting a transcript associated with a influenza virus, or methods of treating an influenza virus nucleoprotein or a clinical condition associated with overexpression or inappropriate expression of an influenza transcript, comprising administering an siRNA in combination with a cationic peptide, wherein said administration may be intravenous or intranasal, or is inhaled, or is delivered by aerosol, or wherein said inhibition is in the lung, or not in the lung, or wherein said combination is delivered with a delivery enhancing agent which may be an antibody or fragment or ligand.

Abe et al. teach targeting an antisense compound to a gene encoding the influenza viral nucleoprotein (NP). Abe et al. teach sequence specific inhibition of expression in vitro using said antisense compounds delivered using liposomes (see Table 2). Abe et al. teach intravenous delivery of antisense compounds to mouse infected with influenza virus and teach a reduction in the viral target mRNA and a decrease in virus titer in the lungs (see pages 65-68). Abe et al. do not teach using a siRNA targeted to a viral nucleoprotein or teach using a siRNA and a cationic peptide, do not teach administration by inhalation or as an aerosol and further do not teach using an antibody or ligand to specifically target a cell.

Tuschl et al. teach the use of siRNA compounds to inhibit gene expression. Tuschl et al. teach siRNA are the new alternative to antisense compounds and have improved efficacy and safety (see page 3). Tuschl et al. teach a method of using siRNA to infect cells of mammals and teach modulating of the function of a target gene in numerous tissues and cells, such as a viral target gene (see page 8). Tuschl et al. teach the siRNA can be delivered using a carrier system (see page 8) and teach the siRNA can be administered by injection or intranasally. Additionally, Tuschl et al. teach a vector capable of expression of a siRNA (see page 7).

Astriab-Fisher et al. teach inhibition of gene expression using oligonucleotides conjugated to cationic peptides. Astriab-Fisher et al. teach one of the major problems with the use of oligonucleotides is delivery to the cytoplasm and nucleus of the cells and teach it was known in the art to try and overcome this problem by complexing the oligonucleotide with liposomes but one major liability with this approach is that liposomes do not work well in the presence of serum and therefore are not effective in vivo situations (see page 83). Astraib-Fisher et al. teach the use of delivery cationic peptides such as Tat protein and Antennapeida protein which are capable of intracellular delivery of molecules across cell membranes (see page 83-85).

Deonarain et al. teach the advantages of using ligand-targeted receptor polyplexes for delivery of nucleic acids to specific cells and tissues. Deonarain et al. teach the use of antibodies that specifically target lung epithelial cells and teach generation of complexes comprising nucleic acids for ligand specific gene delivery (se page 64).

It would have been obvious to one of skill in the art to substitute a siRNA molecule for the antisense molecule in the method of inhibiting an influenza viral gene taught by Abe et al. It would have further been obvious to use the cationic peptide to efficiently deliver the siRNA to the cell of interest and further obvious to incorporate an antibody to the peptide-siRNA complex for targeted delivery to a specific cell type.

It was well known at the time of the instant invention that silencing of gene expression using siRNA was more efficient and sequence specific as compared to antisense or ribozyme technologies. One of ordinary skill in the art would have clearly substituted the antisense compound taught by Abe et al. with a siRNA in a method of inhibiting an influenza viral gene expression in infected organs of a subject. Because it was further well known that one of the major problems with the use of oligonucleotides is delivery to the cytoplasm and nucleus of the cells and well known that using peptide-nucleic acid complexes could overcome these problems, one of ordinary skill in the would have used the cationic peptide as taught by Astriab-Fisher et al. to complex with siRNA in the method of inhibiting an influenza viral gene.

Moreover, one would have incorporated an antibody that specifically targets lung cells into the complex comprising a siRNA and a delivery cationic peptide to specifically target lung cells in methods of targeting an influenza viral gene give Deonarain et al. teach the advantages of using ligand-targeted polyplexes for specifically ensuring certain cells types are targeted with a nucleic acid.

There would have been a reasonable expectation of success at using a cationic peptide for delivery of a siRNA into cells, given Astriab-Fisher et al. teach delivery of a

nucleic acid using a cationic peptide. Further One would have expected to be able to conjugate any antibody onto a peptide-siRNA complex given Deonarain et al. teach how to conjugate a lung specific antibody onto nucleic acid molecule and teach efficient cell targeting properties.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 38-42, 81-83 and 98, 100 and 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al. (US Patent No. 5,194,428), Tuschl et al. (WO 02/44321), Astriab-Fisher et al. teach (Biochemical Pharmacology, 2000. Vol. 60, pp.83-90) and Deonarain et al. (Expert Opinion Ther. Patents 1998, Vol. 8(1): 53-69).

The claims are drawn to methods of inhibiting a transcript associated with a influenza virus, or methods of treating or preventing or treating an influenza virus or a clinical condition associated with overexpression or inappropriate expression of an influenza transcript, comprising administering an siRNA in combination with a cationic polymer, wherein said administration may be intravenous or intranasal, or is inhaled, or is delivered by aerosol, or wherein said inhibition is in the lung, or not in the lung, or wherein said combination is delivered with a delivery enhancing agent which may be an antibody or fragment or ligand.

Agrawal et al. teach targeting an antisense compound to a gene encoding an influenza virus and inhibiting expression of viral PB1 from said gene (see column 5,

lines 5-25). Agrawal et al. teach said antisense compound has at least 8-20 nucleotides that are complementary to the target region and teach administration of the antisense compound intravenously or orally (see column 9). Agrawal et al. does not teach the using a siRNA targeted to a viral PB1 or teach using a siRNA and a cationic polymer and further do not teach using an antibody or ligand to specifically target a cell.

Tuschl et al. teach the use of siRNA compounds to inhibit gene expression. Tuschl et al. teach siRNA are the new alternative to antisense compounds and have improved efficacy and safety (see page 3). Tuschl et al. teach a method of using siRNA to infect cells and teach modulating of the function of a target gene, such as a viral target gene (see page 8). Tuschl et al. teach the siRNA can be delivered using a carrier system (see page 8) and teach the siRNA can be administered by injection or intranasally. Additionally, Tuschl et al. teach a vector capable of expression of a siRNA (see page 7).

Astriab-Fisher et al. teach inhibition of gene expression using oligonucleotides conjugated to cationic peptides. Astriab-Fisher et al. teach one of the major problems with the use of oligonucleotides is delivery to the cytoplasm and nucleus of the cells and teach it was known in the art to try and overcome this problem by complexing the oligonucleotide with liposomes but one major liability with this approach is that liposomes do not work well in the presence of serum and therefore are not effective in vivo situations (see page 83). Astriab-Fisher et al. teach the use of delivery cationic peptides such as Tat protein and Antennapeida protein which are capable of intracellular delivery of molecules across cell membranes (see page 83-85).

Deonarain et al. teach the advantages of using ligand-targeted receptor polyplexes for delivery of nucleic acids to specific cells and tissues. Deonarain et al. teach the use of antibodies that specifically target lung epithelial cells and teach generation of complexes comprising nucleic acids for ligand specific gene delivery (se page 64).

It would have been obvious to one of skill in the art to substitute a siRNA molecule for the antisense molecule in the method of inhibiting viral PB1 gene taught by Agrawal et al. It would have further been obvious to use the cationic peptide to efficiently deliver the siRNA to the cell of interest and further obvious to incorporate an antibody to the peptide-siRNA complex for targeted delivery to a specific cell type.

It was well known at the time of the instant invention that silencing of gene expression using siRNA was more efficient and sequence specific as compared to antisense or ribozyme technologies. One of ordinary skill in the art would have clearly substituted the antisense compound taught by Agrawal et al. with a siRNA in a method of inhibiting an influenza viral gene given Tuschl et al. specifically teach silencing of gene expression is more efficient and sequence specific than with using an antisense compound.

Because it was further well known that one of the major problems with the use of oligonucleotides is delivery to the cytoplasm and nucleus of the cells and well known that using peptide-nucleic acid complexes could overcome these problems, one of ordinary skill in the would have used the cationic peptide as taught by Astriab-Fisher et al. to complex with siRNA in the method of inhibiting an influenza viral gene.

Moreover, one would have incorporated an antibody that specifically targets lung cells into the complex comprising a siRNA and a delivery cationic peptide to specifically target lung cells in methods of targeting an influenza viral gene give Deonarain et al. teach the advantages of using ligand-targeted polyplexes for specifically ensuring certain cells types are targeted with a nucleic acid. Ensuring the siRNA is delivered specifically to the cell of interest would increase the siRNAs capability of mediating RNAi and one of skill in the art would have been motivated to use an antibody coupled to the peptide-siRNA complex.

There would have been a reasonable expectation of success at using a cationic peptide for delivery of a siRNA into cells, given Astriab-Fisher et al. teach delivery of a nucleic acid using a cationic peptide. Further One would have expected to be able to conjugate any antibody onto a peptide-siRNA complex given Deonarain et al. teach how to conjugate a lung specific antibody onto nucleic acid molecule and teach efficient cell targeting properties.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicant's Arguments

Re: Double Patenting

The rejection of claims 38-42, 49, 81-90 and 98-100 as provisionally rejected under the judicially created doctrine of double patenting over claims 12, 22 and 24-27 of

copending Application No. 11/259,434 is maintained for the reasons of record. Applicants have stated they refrain from commenting until such time as the rejection matures into an actual rejection.

Thus claims 12, 22 and 24-27 of co-pending Application No. 11/259,434 anticipates claims 38-42, 49, 81-90 and 98-100 of the instant application.

Re: Claim Rejections - 35 USC § 112

The rejection of claims 38-42 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for the reasons of record in the previous Office action mailed 03/11/2008.

Applicant's arguments filed 09/11/2008 have been fully considered but they are not persuasive. At the outset, the Examiner has not made a typographical error in including claims 38-42 in the rejection and fully intended to reject these claims as stated above. Applicant argues that claims 38-42 are adequately described as claims 81-83, 99 and 100 because they are drawn to inhibition of a target transcript of a respiratory virus in a mammalian subject.

Claims 38-42 are drawn to methods of inhibiting *any transcript associated with influenza virus*, and these claims embrace, at their minimum, siRNA directed to any sequence of any gene expression in any transcript associated with influenza virus, known or yet to be discovered, along with any isoform or allele present within any influenza viral species, or any variant, polymorphic or otherwise, that is within reasonable similarity to these viral families that retain infectivity, such that disease

treatment or prevention is achieved. The instant specification is not considered to have described such breadth of structure linked to such breadth of function because they are drawn to any transcript associated with influenza and is not necessarily limited to inhibiting an influenza virus.

While the instant specification is considered to provide adequate description for methods of inhibiting certain elements of the influenza virus genome using such siRNA/cationic complexes, this is not considered to be representative of the breadth claimed, since at their narrowest, the claims are drawn to methods of inhibiting any transcript associated with any influenza virus. The specification does not provide specific guidance that would allow the skilled artisan to recognize that Applicant was in possession of the instant invention, commensurate in scope with what is now claimed.

Thus, the instantly claimed invention cannot be said to have been adequately described in a way that would convey with reasonable clarity to those skilled in the art that, as of the filling date sought, applicant was in possession of the claimed invention.

Re: Claim Rejections - 35 USC § 103

The rejection of claims 38-42, 49, 81-90 and 98-100 under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al. (US Patent No. 5,194,428), Tuschl et al. (WO 02/44321), Gautum et al. (Molecular Therapy 2000, Vol. 2(1); 63-70) and Kircheis et al. (Gene Therapy 1997: 4: 409-418) is withdrawn.

Re: Claim Rejections - 35 USC § 102

The rejection of claims 38-42, 49, 81-90, 98 and 99 under 35 U.S.C. 102(e) as being clearly anticipated by Beigelman et al. (US Pre-Grant Pub Number 2003/0148928 A1) is withdrawn.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now

contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Kimberly Chong/
Examiner
Art Unit 1635